

# A review of spontaneous closure of ventricular septal defect

Jun Zhang, MD, MS, Jong Mi Ko, BA, Joseph M. Guileyardo, MD, and William C. Roberts, MD

Ventricular septal defect (VSD) is the most common congenital heart malformation and can be detected during the prenatal and postnatal period, in childhood, and in adulthood. Spontaneous closure of VSD can be determined through a variety of methods—echocardiography, Doppler color flow imaging, angiography, auscultation, and cardiac catheterization—and can be proven by pathological evidence at necropsy. There are two major types of VSD, membranous and muscular, as well as the perimembranous variety, which comprises variable portions of the adjacent muscular septum but lacks the membranous septum. VSD appears either as an isolated cardiac defect without other abnormalities or with several complex malformations. It has long been recognized that VSD can close spontaneously, but the incidence of spontaneous VSD closure is still uncertain. Since necropsy study of the hearts with VSD has rarely been reported, information on morphological features of spontaneous VSD closure remains limited. In addition, the mechanisms for spontaneous VSD closure are not fully understood. Herein, we present a brief review of the incidence of spontaneous VSD closure, morphological characteristics of the closure, and the main mechanisms responsible for the closure.

## INCIDENCE OF SPONTANEOUS VSD CLOSURE

The incidence of spontaneous ventricular septal defect (VSD) closure varies greatly, depending on the age and gender of subjects at spontaneous closure, the size and site of the defect, the types of defect, as well as the population studied, methods employed, and length of follow-up period. *Table 1* presents available data on the incidence of spontaneous VSD closure.

**Age and gender.** Age has been found to have a significant influence on the incidence of spontaneous VSD closure, whereas gender seems less likely to affect the incidence. Although spontaneous VSD closure can occur at any age—gestation, infancy, childhood, adolescence, and adulthood (1)—it occurs most commonly during the first 6 months of life (2), during the first year (3, 4), or soon after the first year of life (5). Afterward, the occurrence of closure declines progressively and occurs less commonly after the age of 10 (5). It has been documented that the incidence of the close increases with age, from 24% at 18 months of age to 50% at 48 months and 75% at 120 months (6). However, in older

children, at 3.5 years old, the incidence declines sharply to 44% and then rises to 66% at 7 years and 75% at 10.5 years (6). A similar trend has been found in other reports, which showed 57% (109/190) of cases closed before 3 years of age, 89% (169/190) closed before 8 years of age (7), and 4% to 10% closed after the age of 17 (8, 9). During adulthood, the incidence of spontaneous VSD closure remarkably declines. One study showed that of 188 adults with VSD, 19 patients' (10%) VSD closed spontaneously between the age of 17 and 45 years, and the incidence of closure was greater in the 17- to 24-year age group than the 25- to 34-year group, the 35- to 44-year group, and the  $\geq 45$ -year group (8). Among children, spontaneous VSD closure appears to be predominant in females, but the number of case reports is too small to support the notion (5:3 females vs. males in the report of Farina et al and 20:15 females vs. males from the literature review by Farina et al) (10).

**Size and site.** Several studies have demonstrated that spontaneous VSD closure occurs more frequently in small defects than large ones (3, 7, 11, 12). It was reported that the defects with diameter  $\leq 3$  mm (3),  $< 4$  mm (12) or  $< 5$  or 6 mm (7) were more likely to close spontaneously. The size of the defect has also been suggested to affect the incidence of spontaneous VSD closure, particularly in muscular VSD (2, 3, 13). The incidence of closure varies with the site of the defect, with a closure rate of 83% in the anterior, 84% in the apical, and 89% in the mid-ventricular septum (13). However, there has been a huge controversy over the effects of the defect size on the incidence. Although spontaneous closure of muscular VSD is more frequent in a mid-ventricular defect than an anterior or apical defect (13), apical defects are a preferable location for the closure (2). In addition, there have been no significant differences in spontaneous closure between the mid-muscular and apical defects, although spontaneous closure of apical defects is frequently present (3).

From the Baylor Heart and Vascular Institute (Zhang, Ko, Roberts), the Department of Pathology (Guileyardo, Roberts), and the Division of Cardiology, Department of Internal Medicine (Roberts), Baylor University Medical Center at Dallas.

**Corresponding author:** Jun Zhang, MD, Baylor Heart and Vascular Institute, Baylor University Medical Center at Dallas, 3500 Gaston Avenue, Dallas, TX 75246 (e-mail: jun.zhang@baylorhealth.edu).

**Table 1. Incidence of spontaneous closure of ventricular septal defect (VSD)**

Reference (year)	Incidence	Age at closure and length of follow-up period	Number of patients*	Types of VSDs
1969	25%	Infancy and childhood	—	—
1979	75%	Infants, by 10 years of age	—	All
1979	83%	Infants	—	Muscular
1985	5%	1.5, 6.5, 13, and 14.5 years of age	4/87	Perimembranous
1987	45%	Infants and children, follow-up of 12 months	20/44	Muscular and membranous
1987	37%	Infants and children	7/19	Membranous
1987	17%	Composite group consisting of a hospital and referred patients	11/66	Membranous
1987	50%	Infants and children	5/10	Muscular
1987	22%	Composite group consisting of a hospital and referred patients	7/32	Muscular
1992	76%	Neonates (6 months)	32/42	Muscular
1998	44%	Infants, follow-up of 12 months	490/692	All
1998	71%	Infants, follow-up of 19 years	490/692	All
1998	23%	Children	24/106	—
2000	8%	Infants (3–18 years after birth, median 9.5 years)	8/36	Membranous
2000	74%	Infants (3–18 years after birth, median 9.5 years)	119/161	Muscular
2004	47%	Average age at closure: 9 months	75/159	Perimembranous
2004	83%	Average age at closure: 9 months	29/35	Muscular
2008	23%	Adolescence (mean, 10.6 ± 5.3 years)	11/48	Perimembranous
2010	4%	>16 years	8/200	Perimembranous
2011	84%	Infants (<3 months)	126/150	Muscular
2014	75%	The first year of life	33/44	Muscular

\*Numerator, the number of patients with spontaneous VSD closure; denominator, the number of patients with VSD.

— indicates no information available.

**Types of VSD.** Muscular VSD is believed to be more likely to close spontaneously than membranous VSD (14) or perimembranous VSD (15, 16). It was reported that in 68 children with VSD, 69% (27 of 39) of muscular defects and 28.5% (8 of 28) of perimembranous defects closed spontaneously, indicating that the incidence was significantly greater for muscular defects than for perimembranous defects (15). Meberg et al showed that 74% (119 of 161) of muscular VSD and 22.2% (8 of 36) of membranous VSD closed spontaneously (4). In contrast, Beerman et al reported that of 87 membranous VSDs, only four patients (5%) had spontaneous closure of the defect (17). A recent study of fetal echocardiography showed a high incidence of spontaneous closure of muscular VSD during the first year of life, and 7% (3 of 44) of muscular VSD closed spontaneously in utero (3). The prevalence of spontaneous closure of muscular VSD is not completely understood, but may be related to the inherent structure of the ventricular septum (more complex embryotic origin of the membranous compared to the muscular part) (4), the growth and hypertrophy of surrounding muscular septum in the uterus (3), or a protracted normal closing process in the interventricular septum, because most trabecular septal defects in the neonate period resulted from incomplete trabecular coalescence (2).

## MORPHOLOGICAL CHARACTERISTICS OF SPONTANEOUS CLOSURE OF VSD

Several studies have provided anatomic evidence for spontaneous VSD closure (7, 11, 18–22). Detailed descriptions of morphological characteristics of spontaneous closure for membranous VSD and muscular VSD are summarized in *Tables 2 and 3*. Herein we exemplify some pathological findings. Roberts and his collaborators described anatomic evidence for spontaneous VSD closure, in which 3 membranous VSD in adults and 2 muscular VSD in an adult and a child were included. In the membranous VSD, spontaneous closure resulted from adherence of the septal tricuspid leaflet of the tricuspid valve to the margin of the defect (*Figure 1*). In the muscular VSD, the defect closed entirely by fibrous tissue. A characteristic “jet lesion” of the endocardium was also noted (18, 20). Afterward, several studies provided pathology-proven spontaneous VSD closure at necropsy. A study revealed that the defects closed most commonly by fibrous proliferation, followed by adhesion of the medial leaflet of the tricuspid valve to the defect (7). In 1983, Gaines and Rao reported an adult patient with spontaneous closure of a membranous VSD by adhesion of the septal leaflet of the tricuspid valve to the margins of the defect (21). In the patient reported by Gaines and Rao, a large-sized VSD (1.4 cm in

**Table 2. Anatomic evidence for spontaneous closure of membranous ventricular septal defect (VSD)**

Reference (year)	Type of VSDs	No. of cases	Age (years) and sex	Largest diameter (mm)	Subaortic defect
1962	Membranous	1	86, M	1.5	Subaortic area
1966	Membranous	2	Adults		Subaortic region
1967	Membranous	5	12, 52, 62, 82, 68 (4 F)	7	Subaortic area adjacent to tricuspid valve
1969	Membranous	10	—	—	Subaortic area?
1973	Membranous	1	—	—	Subaortic area
1982	Perimembranous	2	—	—	Subaortic area and confined to trabecular septum
1983	Membranous	1	61, F	14	Inferior portion of membranous septum

— indicates no information available; M, male; F, female.

diameter) was found to locate at the region of the inferior portion of the membranous septum. On the right ventricular aspect of the defect, an aneurysm-like pouch was formed by the adherence of the septal leaflet to the margins of the VSD, and such a pouch could be mistaken for an aneurysm of the membranous septum (21). In 1990, Nir et al provided anatomic evidence of a spontaneous closure of muscular VSD intrauterinely in a neonate (at 5 hours of age) (22). In the neonatal case, gross examination revealed a small depression on the left side of the interventricular muscular septum. Microscopical examination revealed that the defect was completely replaced by fibrotic tissue (22).

#### MECHANISMS RESPONSIBLE FOR SPONTANEOUS VSD CLOSURE

The mechanisms responsible for spontaneous closure of VSD remain unclear; however, multiple factors may be involved. In this regard, distinct or mutual mechanisms may be responsible for membranous VSD, perimembranous VSD, and muscular VSD. *Table 4* summarizes the main proposed mechanisms.

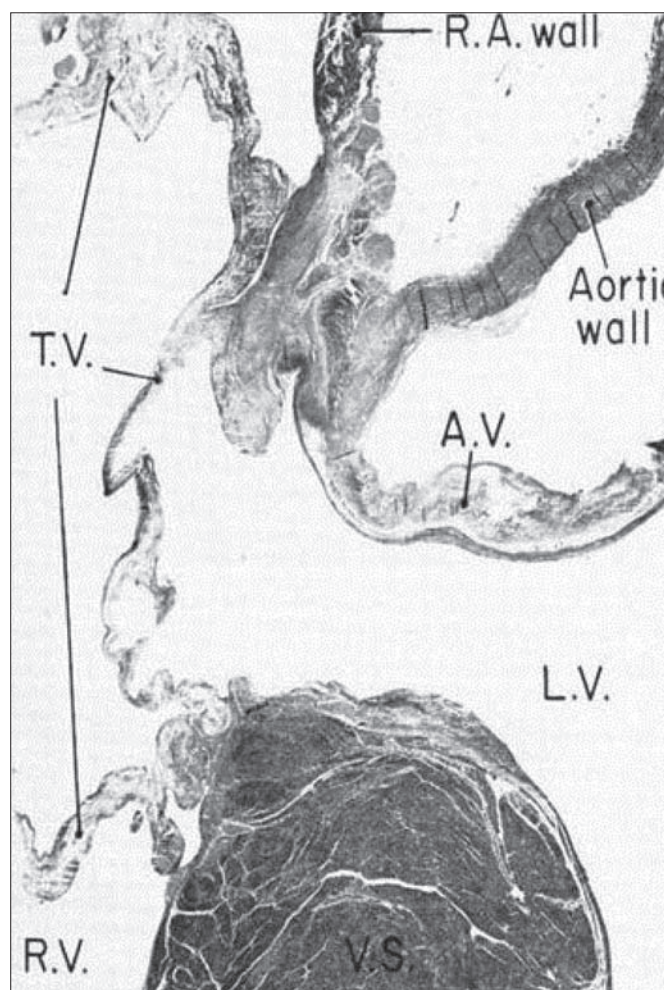
**Table 3. Anatomic evidence for spontaneous closure of muscular ventricular septal defect (VSD)**

Reference (year)	Type of VSD	No. of cases	Age (years) and sex	Size of defect (mm)	Site of defect
1963	Muscular	1	27, M	10	Basal
1963	Muscular	5	—	—	Basal or mid
1966	Muscular	5	Adults	—	Mid
1967	Muscular	3	0 (F), 56 (M), 68 (M)	400 $\mu$	Mid
1967	Muscular	1	3, 27, 1 M, 1 F	10	Basal and mid
1967	Muscular	2	3, 27, 1 F, 1 M	70	Mid
1973	Muscular	2*	—	—	Basal
1990	Muscular	1	Newborn	—	Mid

\*One case was described previously by Simmons et al, 1966.

— indicates no information available; M, male; F, female.

**Membranous VSD.** Roberts and collaborators proposed that a jet lesion functions as a mechanism of spontaneous VSD closure (18, 20). The notion was mainly based on the following pathological observations of the defect: 1) the defect was



**Figure 1.** Photomicrograph showing the membranous ventricular defect closed by fibrous tissue, as viewed in a longitudinal section through the closed defect. AV indicates aortic valve; LV, left ventricle; RA, right atrium; RV, right ventricle; TV, tricuspid valve; VS, ventricular septum. Hematoxylin and eosin stain,  $\times 5$ . Reproduced with permission from the authors (Glancy DL and Roberts WC) and *The American Journal of Medicine*.

**Table 4. Main mechanisms of spontaneous closure of ventricular septal defects (VSD)\***

Category	Mechanism
Membranous VSD	Right ventricular jet lesion
	Adherence of tricuspid valve leaflets
	Aneurysm of membranous septum
	Concept of roughened endothelium
	Left-to-right shunt flow jet toward the tricuspid valve
Perimembranous VSD	Deposition of fibrin over the margins of the defect
	Reduplication of tricuspid valve tissue
	Adherence of tricuspid valve leaflets
	Prolapse of an aortic valve leaflet
	Aneurysm of membranous septum
Muscular VSD	Connective tissue remodeling by matrix metalloproteinase-9
	Growth and hypertrophy of surrounding muscular septum
	Apposition of the edge of defect by fibrous tissue

\*See text for details and references.

located in the outflow portion of the ventricular septum, as viewed from the right ventricle; 2) turbulent flow of blood through a VSD led to a fibrous endocardial reaction; 3) the specific site and physiological alterations of blood resulted in morphological changes of the jet lesion on the adjacent right ventricular endocardium (thickened, pearl-like endocardium); and 4) the above characteristics of the jet lesion made it possible to distinguish this lesion from an aneurysm of the membranous septum (AMS) (18, 20). It was also thought that adhesion of the medial leaflet of the tricuspid valve (18, 20), fibrous tract (incomplete closure), fibrous patch, and AMS may contribute to spontaneous closure of membranous VSD (7). Moe and Gunthroth proposed the concept of endothelial roughening leading to spontaneous closure. It was assumed that a high-velocity jet produced the roughened endothelium, which resulted in a slow accumulation of platelets on the roughened endothelium of the rim of the defect, followed by the jet lesion on the septal leaflet of the tricuspid valve becoming “sticky” and adhering to the rim (23). Takaki et al highlighted the effect of a jet stream, which created the tricuspid pouch. They described several events in sequence: left-to-right shunt flow jet toward the tricuspid valve, followed by deposition of fibrin over the margins of the defect and adhesion of the septal leaflet of the tricuspid valve to the margin of the VSD (24). Recently, Cozijnsen et al presented echocardiography showing a small isolated VSD (with a diameter of 6 mm) in association with a giant AMS (25 mm in length with a diameter of 8 mm), suggesting that the AMS closed the VSD (25).

**Perimembranous VSD.** Anderson et al provided photographs demonstrating the mechanisms of spontaneous closure of perimembranous VSD, in which the reduplication of tricuspid valve tissue, adherence of tricuspid valve leaflets, and prolapse of the aortic valve leaflet were responsible for the closure, but

so-called AMS was rarely present (11). Perimembranous VSD is frequently associated with a so-called AMS. It therefore has been suggested that the association tends to close spontaneously. Beerman et al cautioned that AMS is clearly an inaccurate designation in most cases because morphologically it is not an “aneurysm” and its structure is not the membranous septum (17). Recently, it was found that children with spontaneous closure of perimembranous VSD had higher matrix metalloproteinase-9 levels than the nonclosure group, implying that connective tissue remodeling by matrix metalloproteinase-9 may play an important role in the mechanism of the closure (26).

**Muscular VSD.** It has been suggested that the usual cause of spontaneous closure of muscular VSD is muscular encroachment septal defect plus superimposed fibrosis (27) or physical hypertrophy of the septal myocardium or by fibrous tissue around the margins leading to apposition of the edge of the defect (17). Spontaneous closure may also be attributed to progressive muscular “encroachment” at the margins of the defect with subsequent fibrosis and covering by endocardial proliferation, because VSD, in most cases of tricuspid atresia, is located in the muscular defect, which is surrounded entirely by muscle (1). Another mechanism for closure of muscular VSD is by progressive growth of cardiac tissue from the right ventricular side of the circumference of the defect or by growth and hypertrophy of the surrounding muscular septum (4, 5).

**Tricuspid pouch versus aneurysm of the membranous septum.** Some authors believe that AMS is an important mechanism responsible for spontaneous VSD closure (28, 29). However, the tendency for VSD with an AMS to spontaneously close may be less likely than previously suggested (17). In most cases, the constructive tissue of AMS is usually derived from the tricuspid valve but not from the septal membrane itself (17). In spite of the association between VSD and AMS, Miyake et al suggested that there was no relation between the closure and AMS because AMS was detected in 48% (23 of 48) of patients with perimembranous VSD, and of the 23 defects with AMS, only 4 (17%) closed spontaneously (30). Some authors believe that perimembranous VSD is closed by tricuspid pouch. During the process of natural VSD closure, the septal leaflet of the tricuspid valve forms a large tricuspid pouch (24). The tricuspid pouch closely resembles an AMS by echocardiography and thus the tricuspid pouch can be confused with AMS (24). The tricuspid pouch is created by the effect of a jet stream (24). In contrast, AMS is formed by projection of the left ventricular pressure during spontaneous closure of a VSD (24, 31).

1. Rao PS. Natural history of the ventricular septal defect in tricuspid atresia and its surgical implications. *Br Heart J* 1977;39(3):276–288.
2. Hiraishi S, Agata Y, Nowatari M, Oguchi K, Misawa H, Hirota H, Fujino N, Horiguchi Y, Yashiro K, Nakae S. Incidence and natural course of trabecular ventricular septal defect: two-dimensional echocardiography and color Doppler flow imaging study. *J Pediatr* 1992;120(3):409–415.
3. Erol O, Sevet O, Keskin S, Yazıcıoğlu HF, Gül A. Natural history of prenatal isolated muscular ventricular septal defects. *J Turk Ger Gynecol Assoc* 2014;15(2):96–99.
4. Meberg A, Otterstad JE, Frøland G, Lindberg H, Sørland SJ. Outcome of congenital heart defects—a population-based study. *Acta Paediatr* 2000;89(11):1344–1351.

5. Krovetz LJ. Spontaneous closure of ventricular septal defect. *Am J Cardiol* 1998;81(1):100–101.
6. Alpert BS, Cook DH, Varghese PJ, Rowe RD. Spontaneous closure of small ventricular septal defects: ten-year follow-up. *Pediatrics* 1979;63(2):204–206.
7. Collins G, Disenhouse R, Keith JD. Spontaneous closure of ventricular septal defect. *Can Med Assoc J* 1969;100(16):737–743.
8. Neumayer U, Stone S, Somerville J. Small ventricular septal defects in adults. *Eur Heart J* 1998;19(10):1573–1582.
9. Soufflet V, Van de Bruaene A, Troost E, Gewillig M, Moons P, Post MC, Budts W. Behavior of unrepaired perimembranous ventricular septal defect in young adults. *Am J Cardiol* 2010;105(3):404–407.
10. Farina MA, Hook EB. Apparent sex difference in spontaneous closure of ventricular septal defect. *J Pediatr* 1978;93(6):1065–1066.
11. Anderson RH, Lenox CC, Zuberbuhler JR. Mechanisms of closure of perimembranous ventricular septal defect. *Am J Cardiol* 1983;52(3):341–345.
12. Tomita H, Arakaki Y, Yagihara T, Echigo S. Incidence of spontaneous closure of outlet ventricular septal defect. *Jpn Circ J* 2001;65(5):364–366.
13. Miyake T, Shinohara T, Inoue T, Marutani S, Takemura T. Spontaneous closure of muscular trabecular ventricular septal defect: comparison of defect positions. *Acta Paediatr* 2011;100(10):e158–e162.
14. Shirali GS, Smith EO, Geva T. Quantitation of echocardiographic predictors of outcome in infants with isolated ventricular septal defect. *Am Heart J* 1995;130(6):1228–1235.
15. Turner SW, Hunter S, Wyllie JP. The natural history of ventricular septal defects. *Arch Dis Child* 1999;81(5):413–416.
16. Miyake T, Shinohara T, Nakamura Y, Fukuda T, Tasato H, Toyohara K, Tanihara Y. Spontaneous closure of ventricular septal defects followed up from <3 months of age. *Pediatr Int* 2004;46(2):135–140.
17. Beerman LB, Park SC, Fischer DR, Fricker FJ, Mathews RA, Neches WH, Lenox CC, Zuberbuhler JR. Ventricular septal defect associated with aneurysm of the membranous septum. *J Am Coll Cardiol* 1985;5(1):118–123.
18. Roberts WC, Morrow AG, Mason DT, Braunwald E. Spontaneous closure of ventricular septal defect, anatomic proof in an adult with tricuspid atresia. *Circulation* 1963;27:90–94.
19. Simmons RL, Moller JH, Edwards JE. Anatomic evidence for spontaneous closure of ventricular septal defect. *Circulation* 1966;34(1):38–45.
20. Glancy DL, Roberts WC. Complete spontaneous closure of ventricular septal defect: necropsy study of five subjects. *Am J Med* 1967;43(6):846–853.
21. Gaines JJ, Rao RN. Closure of membranous ventricular septal defect of heart by septal leaflet of tricuspid valve. *Hum Pathol* 1983;14(12):1082–1084.
22. Nir A, Weintraub Z, Oliven A, Kelener J, Lurie M. Anatomic evidence of spontaneous intrauterine closure of a ventricular septal defect. *Pediatr Cardiol* 1990;11(4):208–210.
23. Moe DG, Guntheroth WG. Spontaneous closure of uncomplicated ventricular septal defect. *Am J Cardiol* 1987;60(8):674–678.
24. Takaki A, Ogawa H, Wakeyama T, Iwami T, Kimura M, Uchinoumi H, Akashi S, Matsuda S, Miyazaki Y, Matsuzaki M, Okada H, Nishida M, Murakami M. Tricuspid pouch can cause systemic embolization in adulthood. *Circ J* 2006;70(5):631–633.
25. Cozijnsen MA, Cozijnsen L, Maas AC, Bakker-de Boo M, Bouma BJ. A ventricular septal defect with a giant appendiform aneurysm of the membranous septum. *Neth Heart J* 2013;21(3):152–154.
26. Cheng KS, Liao YC, Chen MY, Kuan TC, Hong YH, Ko L, Hsieh WY, Wu CL, Chen MR, Lin CS. Circulating matrix metalloproteinase-2 and -9 enzyme activities in the children with ventricular septal defect. *Int J Biol Sci* 2013;9(6):557–563.
27. Suzuki H, Lucas RV Jr. Spontaneous closure of ventricular septal defects. Anatomic evidence in three patients. *Arch Pathol* 1967;84(1):31–36.
28. Varghese PJ, Rowe RD. Spontaneous closure of ventricular septal defects by aneurysmal formation of the membranous septum. *J Pediatr* 1969;75(4):700–703.
29. Misra KP, Hildner FJ, Cohen LS, Narula OS, Samet P. Aneurysm of the membranous ventricular septum. A mechanism for spontaneous closure of ventricular septal defect. *N Engl J Med* 1970;283(2):58–61.
30. Miyake T, Shinohara T, Fukuda T, Ikeoka M, Takemura T. Spontaneous closure of perimembranous ventricular septal defect after school age. *Pediatr Int* 2008;50(5):632–635.
31. Baron MG, Wolf BS, Grishman A, van Mierop LHS. Aneurysm of the membranous septum. *Am J Roentgenol Radium Ther Nucl Med* 1964;91:1303–1314.